STATISTICAL ANALYSIS PLAN

D1002002

A Long-Term Study of SM-13496 in Subjects with Bipolar I Disorder

AUTHOR: ████████

VERSION NUMBER AND DATE: V1.0, 20MAR2018

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 20MAR2018) for Protocol D1002002.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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OUTPUT TEMPLATES SIGNATURE PAGE

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
0.1	16AUG2016		Not Applicable – First Version
0.2	18OCT2016		Updates made based on comments received from the Sponsor.
0.3	13OCT2017		Updates made based on comments received from the Sponsor for Dry Run 1 and on final decisions for previous double-blind study (D1002001).
0.4	28NOV2017		Updates made based on comments received from the Sponsor to the previous draft version.
0.5	06MAR2018		Updates made based on comments received from the Sponsor for Dry Run 2 and to incorporate references to: - Changes from Planned Analysis in the Protocol - Definition of Week 28 cut-off timepoint - New summaries requested by the Sponsor for Japanese subjects regarding their index episode (Major vs. Non-Major Depressive Episode)
1.0	20MAR2018		Final version.

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol D1002002. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol D1002002 Version 1.04, dated 15th March 2016.

2. STUDY OBJECTIVES

The study objective is to evaluate the long-term efficacy and safety of SM-13496 (20-120 mg/day) in subjects with bipolar I disorder.

2.1. EFFICACY OBJECTIVES

The following efficacy objectives will be analyzed throughout the study up to Week 28 outside Japan and Week 52 within Japan, unless otherwise specified:

1) Change from baseline in the prior double-blind study (D1002001) and the present study (D1002002):

- Montgomery-Åsberg Depression Rating Scale (MADRS) total score

- Young Mania Rating Scale (YMRS) total score

- Clinical Global Impressions Bipolar Version, Severity of Illness (CGI-BP-S) (overall, depression, mania) scores

- Sheehan Disability Scale (SDS) score

- Hamilton Rating Scale for Anxiety (HAM-A) total score

2) Time to recurrence/relapse of any mood event from clinical stability of bipolar disorder

3) Time to all cause discontinuation

2.2. SAFETY OBJECTIVES

The following safety objectives will be analyzed throughout the study up to Week 28 outside Japan and Week 52 within Japan, unless otherwise specified:

1) Incidence of adverse events (AEs) and adverse drug reactions (ADRs)

2) Incidence of extrapyramidal AEs and ADRs

3) Proportion of subjects with concomitant use of antiparkinson medication

4) Change from baseline in the prior double-blind study (D1002001) and the present study (D1002002):

- Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) total scores (except for the overall severity score)

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- DIEPPS individual symptoms scores

- Serum prolactin concentration

- ECG parameter (QTc)

- Fasting blood glucose, HbA1c (NGSP), glycoalbumin, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides

- Body weight (kg)

5) Laboratory measures and vital signs

6) Proportion of subjects with any instance of suicide attempt or suicidal ideation based on the Columbia-Suicide Severity Rating Scale (C-SSRS)

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

The study will be conducted in a multi-center and open-label manner.

The study is a long-term study to evaluate the efficacy and safety of SM-13496 (Lurasidone) at doses of 20-120 mg/day orally once daily. The dose of SM-13496 can be increased or decreased by 20mg/day at the scheduled visits and any unscheduled visit at least 7 days after the prior visit.

The primary variable for assessing ongoing efficacy will be the change in the MADRS total score, and the duration of treatment will be 28 weeks outside Japan and 52 weeks within Japan.

3.2. SAMPLE SIZE

The targeted number of subjects enrolled in this study will be as follows:

- Subjects who completed the prior double-blind study: 325 subjects

- Subjects who did not participate in the prior double-blind study: 80 subjects (Japan only)

Rationale:

The percentage of subjects who completed PREVAIL 2 study, which has a study design similar to that of the present study, was 74%. On the basis of the results of the PREVAIL 2 study, the percentage of subjects who complete the prior double-blind study and who will enroll in to the present study is estimated at approximately 65%. From considerations of study duration and enrollment speed, approximately 80 Japanese subjects will be expected to enroll in the present study.

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3.3. TREATMENT GROUPS

Treatment groups will be assigned per subject based on a combination of the treatment group randomized to in the prior double-blind study (D1002001) and the current study (D1002002) as follows:

- Subjects in the 20-60 mg group, presented as LUR20-LUR

- Subjects in the 80-120 mg group, presented as LUR80-LUR

- Subjects in either the 20-60 mg group or the 80-120 mg group, presented as LUR-LUR

- Subject in the placebo group, presented as PBO-LUR

- Subjects who did not participate in the prior study, therefore no treatment assignment in the prior double-blind study, presented as NR-LUR

- All subjects in the long-term study, presented as ALL-EXT

3.4. STUDY FLOW CHART

Table A: **Study Flow Chart for completers of the placebo-controlled study (D1002001)**
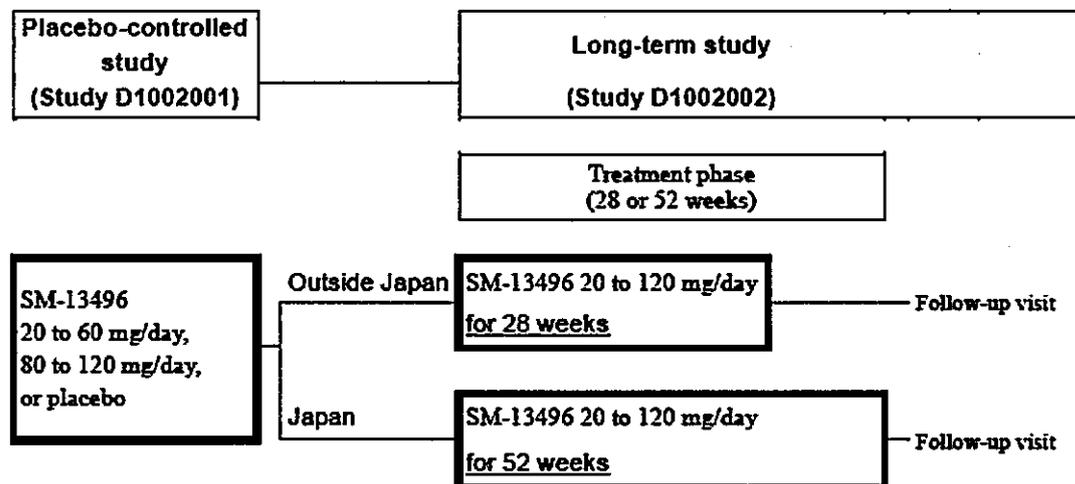
Assessment at Week 6 in the placebo-controlled study will be used for baseline in the long-term study.
The subjects will visit the study site for a follow-up visit 14 days (± 7 days) after completion or discontinuation.

Table B:**Study Flow Chart for Subject who did not Participate in the Placebo-controlled Study (in Japan only)**

Screening phase (1-14 days)	Treatment phase (52 weeks)

Screening	SM-13496 20 to 120 mg/day for 52 weeks adjunctive to either lithium or VPA	— Follow-up visit
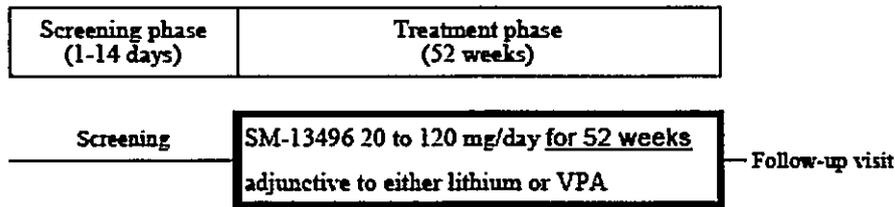
VPA: valproate/divalproex

The subjects will visit the study site for a follow-up visit 14 days (± 7 days) after completion or discontinuation.

3.5. SCHEDULE OF EVENTS

Schedule of events can be found in Section 3.2 of the protocol.

3.6. CHANGES TO ANALYSIS FROM PROTOCOL

The only changes from the planned analysis stated in the protocol (V1.04, Dated 15MAR2016) are related to the subgroup analysis.

- Subgroups to consider: In section 9.5.3 of the protocol, the categories stated for the analysis by mood stabilizer are Lithium, VPA or None. Another category for "Both" (Lithium and VPA) is needed, according to the data collected.

- Efficacy subgroup analysis: Section 9.5.3 in the protocol states that *"Subgroup analysis will be conducted for the change from DB and LT baselines in efficacy variables, such as the MADRS total score, the YMRS total score, the CGI-BP-S score (overall, depression, mania) and the HAM-A total score, as well as for the time to recurrence/relapse and time to all cause discontinuation, whenever appropriate."*. Subgroup analysis have been included for the above variables with the only exception of the Hamilton Rating Scale for Anxiety (HAM-A).

- Safety subgroup analysis: In addition to the analysis stated in section 9.6.6 of the protocol for the safety variables, mood stabilizer and most recent or current episode subgroup analysis have also been conducted for the Columbia Suicide Severity Rating Scale (C-SSRS).

As per additional request, not initially contemplated in the protocol, a set of summaries containing disposition, demographic and baseline characteristics, exposure and compliance, efficacy and safety data will be added for Japanese subjects by most recent or current episode subgroup, splitting by presence or absence of a Major depressive episode. The details of these summaries are included in section 18 of the current document.

4. PLANNED ANALYSES

Only Final Analysis will be performed for this study.

4.1. DATA MONITORING COMMITTEE (DMC)

There will be no DMC for this study.

4.2. INTERIM ANALYSIS

No interim analysis is planned.

4.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by ████████████ following Sponsor Authorization of this Statistical Analysis Plan, Database Lock and Sponsor Authorization of Populations.

5. ANALYSIS POPULATIONS

Agreement and authorization of subjects included/ excluded from each analysis population will be conducted prior to Database Lock. The populations will be summarized for each treatment group.

5.1. ALL ENROLLED POPULATION [ENR]

The all enrolled population will consist of all subjects who provided informed consent for the long-term study.

5.2. SAFETY POPULATION [SAF]

The safety population will consist of all subjects included in the all enrolled population who received at least one dose of the study medication in the long-term study (D1002002).

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date, and will be used to show start/ stop day of assessments and events.

Reference start date is defined as the day of the first dose of study medication, (Day 1 is the day of the first dose of study medication of the long-term study).

- If the date of the event is on or after the reference start date then:

Study Day = (date of event − reference start date) + 1.

- If the date of the event is prior to the reference start date then:

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Study Day = (date of event − reference start date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in Appendix 2: Partial Date Conventions.

6.2. BASELINE

For subjects who completed the prior double-blind study, the double-blind baseline (DB baseline) is defined as the last non-missing assessment (including unscheduled assessments) collected on or prior to the reference start date of the prior double-blind study (D1002001). In the case where the last non-missing assessment and the reference start date coincide, that assessment will be considered pre-baseline, but AEs and medications commencing on the reference start date will be considered post-baseline. The long-term baseline (LT baseline) is defined as Week 6 of the prior double-blind study (D1002001).

For subjects who did not participate in the prior double-blind study, DB baseline is not defined, and LT baseline is defined as the last non-missing assessment (including unscheduled assessments) collected on or prior to the reference start date of the long-term study (D1002002). In the case where the last non-missing assessment and the reference start date coincide, that assessment will be considered pre-baseline, but AEs and medications commencing on the reference start date will be considered post-baseline.

Post-baseline data will be defined as non-missing data on or after Day 1 and through 7 days after the final administration of study medication in the treatment phase (excluding baseline).

In the event that data recorded in the prior double-blind study (D1002001) would actually be collected after the reference start date of the long-term study (D1002002), this data will be included in this long-term study in looking for maximum on treatment values, but will not be taken into account for any other summaries.

6.3. DERIVED TIMEPOINTS

6.3.1. LAST OBSERVATION CARRIED FORWARD (LOCF) TIMEPOINT

The last non-missing post-baseline assessment during the treatment phase will be carried forward and will be defined as the last non-missing assessment (scheduled or unscheduled) up to 7 days after the last dose of study medication. Follow-up visits and assessments that are collected beyond 7 days after the last dose of study medication will be excluded from the LOCF derivation. Unscheduled visits are considered usable for derivation of the LOCF endpoint in all domains where LOCF is required.

Week 28 (LOCF) endpoint and Week 52 (LOCF) endpoint (subjects within Japan only) will be derived based on the derivation above.

Week 28 (LOCF) endpoint for subjects within Japan who early terminate the study prior to Week 28 will be derived based on the derivation above. For subjects within Japan who participate in the study after Week 28, the Week 28 visit should be used as Week 28 (LOCF) endpoint.

6.3.2. WEEK 28 CUT-OFF TIMEPOINT

Data regarding treatment exposure and compliance, as well as efficacy and safety data, will be presented for all subjects up to Week 28 and will be repeated for all Japanese subjects up to Week 52. Details on the specific

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analysis are indicated in the applicable analysis sections further in this document.

For the Week 28 summaries, a data cut-off will be applied for all Japanese subjects who continue in the study to Week 52. The cut-off date to be used will be the date of the Week 28 visit for each subject.

6.4. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Post-baseline unscheduled assessments will not be included in by-visit summaries, but will contribute to the baseline, LOCF endpoint value, or best/ worst case value where required (e.g. shift table).

No retests (same visit number assigned) are expected.

The data collected at early termination (ET) visit will be mapped to the next scheduled visit from the actual discontinuation date. Data collected at the early termination visit will be eligible for LOCF in cases where the study is not completed, provided the early termination is within 7 days of the last dose of study medication.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.5. WINDOWING CONVENTIONS

There will be no visit windowing for the analyses performed for this study. All data will be organized and analyzed according to the scheduled times as outlined in the protocol and by the visit denoted on the electronic Case Report Form (eCRF).

If subjects terminate the study early and the ET visit occurs within 7 days after the last dose of study medication, the assessment information will be assigned to the next scheduled visit. This will apply to all the safety and efficacy endpoints to be analyzed.

All tables and figures presenting data by visit will present only those timepoints where the applicable assessment was scheduled to be collected. Unscheduled and early termination data will only be included for definition of LOCF endpoint or overall assessments. Data listings will present all data regardless of visit.

6.6. STATISTICAL TESTS

The default significance level will be (5%); confidence intervals will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

6.7. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Change from Baseline = Post-baseline Test Value at Visit X – Baseline Value

6.8. SOFTWARE VERSION

All analyses will be conducted using SAS (UTF-8 encoding) version 9.4 or higher.

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7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

No adjustment for covariates and factors will be done for this study.

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers internationally.

7.3. MISSING DATA

Missing efficacy data will be handled as described in Section 16.1.3 Missing Data Methods for Efficacy variable(s) of this analysis plan.

Missing safety data will be subject to LOCF analysis as specified in relevant safety domain sections.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

The study has no hypotheses and therefore no adjustment for multiplicity is needed.

7.5. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted for the change from DB and LT baselines to Week 28 (LOCF) or Week 52 (LOCF) endpoint for the efficacy variables, such as the MADRS total score, the YMRS total score, the CGI-BP-S score (overall, depression, mania), the HAM-A total score, as well as the time to recurrence/relapse of any mood event from clinical stability of bipolar disorder and time to all-cause discontinuation. Selected subgroup analysis will be repeated for the subjects enrolled in Japan as indicated in the applicable analysis sections.

Selected subgroup analysis will be repeated for the safety analysis as indicated in the applicable safety analysis sections.

The following subgroups will be assessed and described within the analysis sections:

- Sex:

  o Male
  o Female

- Age (years):

  o <55
  o ≥55
  And

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- o   <65
- o   ≥65

- Mood stabilizer:

  - o   Lithium
  - o   VPA
  - o   Both
  - o   None

- Psychotic features:

  - o   With
  - o   Without

- Most recent or current episode:

  - o   Major depressive episode
  - o   Manic episode
  - o   Mixed episode
  - o   Hypomanic episode

- Bipolar I Diagnosis Subtype:

  - o   Rapid cycling
  - o   Non-rapid cycling

- Country:

  - o   Japan
  - o   Malaysia
  - o   Philippines
  - o   Russia
  - o   Taiwan
  - o   Ukraine
  - o   Lithuania
  - o   Slovakia

8. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by ███████.

Summaries for categorical data will include frequency counts and percentages. Subjects with missing data will not be included in the calculations of percentages, unless otherwise specified. For continuous data points, summaries will include a count (n), mean, standard deviation (SD), median, minimum and maximum.

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9. DISPOSITION AND WITHDRAWALS

Subject disposition will be summarized for the all enrolled population, by treatment group.

The number and percentage of subjects screened, screen failed, treated, completed and discontinued will be summarized, along with the primary reason for discontinuation.

Important protocol deviations will be identified programmatically and also manually, and will be subject to medical review as part of the Blind Data Review Meeting (BDRM) prior to database hard lock. Important protocol deviations will be summarized for the all enrolled population, by treatment group. This summary will be presented for all patients overall, and repeated by country.

Inclusion/exclusion criteria will only be listed for the all enrolled population, by treatment group.

The safety analysis population will be presented for the all enrolled population, by treatment.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics summaries will be presented for the safety population by treatment group. Listings will include all enrolled subjects.

No statistical testing will be carried out for demographic or other baseline characteristics.

Summaries will include subjects who completed the prior double-blind study and entered the long-term study, as well as subjects who did not participate in the prior double-blind study and entered the long-term study only. Demographics and baseline characteristics will be carried over from the prior double-blind study for subjects who completed the prior double-blind study.

The following demographic and other baseline characteristics will be summarized and listed. Data points donated by * are reported in a listing only:

1) Demographics

- Age (years)

- Sex

- Race

- Ethnicity

- Height (cm)

- Country

- Weight (kg)

- Body Mass Index (BMI) (kg/m^2)

2) Other Baseline Characteristics

- Baseline Mood Stabilizer

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- o Lithium (mmol/L)
- o VPA (mg/L)
- LT Baseline scores

  - o MADRS total score
  - o CGI-BP-S depression score
  - o CGI-BP-S mania score
  - o CGI-BP-S overall score
  - o YMRS total score

3) Disease data

- Date of initial onset of bipolar I disorder*

- Age at initial onset of bipolar I disorder*

- DSM-IV-TR diagnostic code (regarding severity/psychotic/remission specifiers) of the current major depressive episode or other current episode*

- Date of onset of the current episode*

- Presence or absence of characteristics of rapid cycling disease course

- Number of mood episodes for the consequent 12 months, by episode type

- Date of onset of the most recent major depressive, manic, mixed or hypomanic episode*

- Date of most recent hospital discharge if hospitalized because of major depressive, manic, mixed or hypomanic episodes*

- Number of hospitalizations due to bipolar I disorder (0, 1, 2 or more)

- Psychiatric disease other than bipolar I disorder; diagnosis, DSM-IV-TR diagnostic code, date of onset*

11. SURGICAL AND MEDICAL HISTORY

Medical History information summaries will be presented for the safety population by treatment group. Listings will include all enrolled subjects.

Summaries will include subjects who completed the prior double-blind study and entered the long-term study, as well as subjects who did not participate in the prior double-blind study and entered the long-term study only. Surgical and Medical History will be carried over from the prior double-blind study for subjects who completed the prior double-blind study.

- Medical History will be coded using **MedDRA Version 19.1**

  - o Medical History conditions are defined as those conditions beginning prior to screening which stop prior to/are ongoing at Screening
  - o Summarized by System Organ Class (SOC) and Preferred Term (PT)

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12. PSYCHIATRIC HISTORY

Psychiatric history results, including DSM-IV-TR bipolar subtype diagnosis, are recorded on the eCRF, and will be summarized for the safety population, by treatment group. Number and percent of subjects reporting each DSM-IV-TR subtype will be presented. Listings will include all enrolled subjects.

Summaries will include subjects who completed the prior double-blind study and entered the long-term study, as well as subjects who did not participate in the prior double-blind study and entered the long-term study only. Psychiatric history will be carried over from the prior double-blind study for subjects who completed the prior double-blind study.

The following will be summarized descriptively:

- Most recent / current Episode of Bipolar I Disorder

    o Major depressive episode
    o Manic episode
    o Mixed episode
    o Hypomanic episode

- Bipolar I disorder cycling within 12 month (0-3, 4-7 or ≥ 8)

- Psychotic features of bipolar I history

- Age at initial onset of bipolar I in years

- Duration of bipolar I from initial onset to screening in years

- Duration of bipolar I from onset of current episode to screening in weeks

- Number of prior hospitalizations for bipolar I disorder (0, 1, ≥ 2)

- Duration since discharge from last hospitalization for each type of episode to screening in months

- Number of mood episodes for the consequent 12 months, by episode type

- Subjects with other psychiatric disorders present

Incidence of other Current Psychiatric Diagnoses will be summarized by DSM-IV Code subtype for the safety population by treatment group.

13. CONCOMITANT MEDICATIONS

Concomitant medications summaries will be presented for the safety population and coded using **WHO Drug Dictionary Enhanced /WHO Herbal Dictionary v01DEC2013.** Listings will include all enrolled subjects.

Summaries will include subjects who completed the prior double-blind study and entered the long-term study, as well as subjects who did not participate in the prior double-blind study and entered the long-term study only.

ATC coding will be performed for the study, including screen failed subjects. Medications will be summarized using ATC level 3 coding and Preferred Term.

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See Appendix 2 for handling of partial dates for medications. In the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified as both prior and concomitant.

- 'Prior' medications are medications which started prior to the first dose of study medication in the long-term study (D1002002) or have a missing medication start date. If they are ongoing at the start of study medication then the medication will be classified as prior and concomitant. For subjects who completed the prior double-blind study, prior medications are medications recorded during the double-blind study prior to the first dose of study medication in the long-term study.

- 'Concomitant' medications are medications which:

  o started prior to, on or after the first dose of study medication in the long-term study or have a missing medication start date

  o AND ended on or after the date of first dose of study medication in the long-term study or were ongoing at the end of the long-term study.

- 'Post' medications are medications which started on the same day or after the end of study medication administration in the long-term study.

A summary of subjects with concomitant use of antiparkinson medication will be summarized by treatment group. Additional summaries will be produced categorizing medication categories related to Mood Stabilizers, Anxiolytics and Hypnotics.

14. EXPOSURE

14.1. STUDY MEDICATION

Exposure to study medication in days will be presented for the safety population by treatment group.

Summaries of exposure will be based on the first and last study medication administration dates, rather than the blister card information. The first and last study medication administration dates will be taken from the eCRF drug administration and accountability form. Return of the blister card at any given visit is not a prerequisite for inclusion in exposure summary statistics if corresponding dose start and end dates are reported.

The mean daily dose (overall) will be summarized for the safety population by treatment group stratified for all subjects and completers. Completers are defined as follows:

- Week 28: All subjects who completed Week 28. For Japanese subjects Week 28 cut-off will be applied.

- Week 52 (Japan only): All Japanese subjects who completed Week 52.

The modal daily dose (overall and between visits) will likewise be summarized based on the overall study medication exposure. In addition, the number and percentage of subjects receiving the maximum doses of 20 mg, 40 mg, 60mg, 80 mg, 100 mg and 120 mg will be summarized by visits.

The number and percentage of subjects will be summarized for the following exposure duration categories:

- >=1 day, 7, 14, 28, 56, 84, 112, 140, 168, 196, 224, 252, 280, 308, 336, and 364 respectively

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- 1-6, 7-13, 14-27, 28-55, 56-83, 84-111, 112-139, 140-167, 168-195, ..., and 336-364 days

Shift in dose level (SM-13496 20mg, 40mg, 60mg, 80mg, 100mg, 120mg) from the previous scheduled visit to the current scheduled visits will be summarized by each visit.

Return of the blister card at any given visit is not a prerequisite for inclusion in mean daily dose, modal daily dose calculations or dose change summary statistics, if corresponding first and last study medication administration dates are reported.

Exposure to study medication will be presented for all subjects up to Week 28 and repeated for all Japanese subjects up to Week 52 separately. Dose change from previous visit and compliance will be presented for all subjects overall.

14.2. SERUM LITHIUM AND VPA

Observed and changes from LT baseline in serum concentration of lithium (mmol/L) and of VPA (mg/L) will be summarized at each visit, and Week 28 (LOCF) and Week 52 (LOCF) endpoints (subjects within Japan). As an aid to interpretation of serum levels, a summary of exposure to each drug will be provided, and will include the following: prior total daily dose at screening (mmol/L for lithium and mg/L for VPA), total daily dose at LT baseline and each visit, and changes from LT baseline up through Week 28 (LOCF) endpoint and Week 52 (LOCF) endpoint. The analyses above will be conducted using the safety population.

For the purpose of summarizing exposure to lithium, different formulations of lithium are assumed to be equivalent.

14.3. DERIVATIONS

Cumulative dose (mg) = Sum of all the doses the subject is expected to take during the study.

Duration of exposure (days) = (date of last study medication administration – date of first study medication administration) + 1.

Interruptions, compliance, and dose changes are not taken into account for duration of exposure.

Mean daily dose (mg/day) of study medication = Cumulative dose (mg)/Duration of exposure (days).

The modal daily dose (mg/day) is defined as the daily dose that is taken for the most time for each study phase, in terms of number of days among all doses taken. If there are ties, therefore more than one modal daily dose for a subject, the last modal dose administered will be used in the summaries.

The modal daily dose (mg/day) between visits is calculated similarly to the modal daily dose for overall. Therefore, the dose that is taken for the most time from the visit date to the day prior to the next visit date.

15. STUDY MEDICATION COMPLIANCE

Compliance will be presented for the safety population by treatment group, both continuously (mean percentage) and categorically (compliant versus non-compliant, non-compliant <75% and non-compliant >125%, and subjects with any missing compliance).

15.1. DERIVATIONS

At each visit, prior to dispensing study medication, previously dispensed study medication will be retrieved and assessed by tablet count. Compliance will be calculated overall as follows:

- Percent compliance = (number of tablets taken / number of tablets should have taken) x 100.

- Number of tablets taken = number of tablets dispensed – number of tablets returned. Lost tablets are considered to have been returned for the purpose of calculating compliance.

- Number of tablets should have taken = (number of tablets supposed to take in a day) x (number of exposure days).

If the number of tablets returned is missing, compliance will be missing. Non-compliance is defined as less than 75% or more than 125% non-missing overall compliance with the study medication. Subjects with missing compliance are not classified as non-compliant, and are not considered to be protocol deviators.

16. EFFICACY OUTCOMES

16.1. EFFICACY

The efficacy analysis will be performed for the safety population by treatment group. Listings will include all enrolled subjects.

16.1.1. EFFICACY VARIABLE & DERIVATION

16.1.1.1. Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS is a clinician-rated assessment of the subject's level of depression, measured at Screening, Baseline, Week 1 to Week 28 (for subject outside Japan) and Week 1 to Week 52 for subject in Japan.

The measure contains 10 items that measure apparent and reported sadness, inner tension, reduced sleep and appetite, difficulty concentrating, lassitude, inability to feel, and pessimistic and suicidal thoughts. Each item is scored in a range of 0 to 6 points, with higher scores indicating increased depressive symptoms. The MADRS total score is the sum of all 10 items scores and can be obtained from the eCRF directly.

The total score is calculated as the sum of all the component scores of the MADRS scale. The MADRS total score ranges from 0 to 60. Higher scores are associated with greater severity of Bipolar I disorder.

16.1.1.2. Young Mania Rating Scale (YMRS)

The YMRS is an 11-item instrument used to assess the severity of mania in subjects with a diagnosis of bipolar disorder, measured at Screening, Baseline, Week 1 to Week 28 for subject outside Japan and Week 1 to Week 52 for subject within Japan.

The 11 items are: Elevated Mood, Increased Motor Activity Energy, Sexual Interest, Sleep, Irritability, Speech (Rate and Amount), Language-Thought Disorder, Content, Disruptive-Aggressive Behavior, Appearance, and Insight. The YMRS is a clinician-rated assessment. Seven items are rated on a 5-point scale, ranging from 0 to 4, and four items are rated on a 9-point scale, ranging from 0 to 8. The YMRS uses operationally-defined anchor

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points and the normal expected score is >20. Ratings are based on subject self-reporting, combined with clinician observation (accorded greater score).

The YMRS total score is the sum of the 11 individual items and ranges from 0 to 60. Higher scores are associated with a greater severity of mania. If one or more items are missing at a visit, the total score will be set to missing.

16.1.1.3. Clinical Global Impressions Scale – Bipolar Version - Severity of Illness (CGI-BP-S)

The CGI-BP-S is a clinician-rated assessment of the subject's current illness state (mania, depression, and overall bipolar illness), measured at Screening, Baseline, Weeks 1 to Week 28 for subject outside Japan and Week 1 to Week 52 for subject within Japan.

A clinician assesses the subject's current illness on a 7-point scale ranging from 1= 'Normal, not ill' to 7= 'Very severely ill'. Higher scores are associated with greater illness severity.

16.1.1.4. Sheehan Disability Scale (SDS)

The SDS is a composite of 5 self-rated items designed to measure the extent to which 3 major sectors in the subject's life are impaired by depressive symptoms, measured at Screening, Baseline, Weeks 4, 12, 20 and 28 for subject outside Japan and Weeks 4, 12, 20, 28, 36, 44 and 52 for subject within Japan.

Three items are self-rated using a 10-point visual analog scale ranging from 0 to 10 to assess disability across three domains: work/school, social life, and family life. The three items will be summarized individually in addition to the SDS total score. The final two items ask patients about the number of days on which their symptoms caused them to miss school and/or work and the number of days on which their symptoms caused them to be underproductive at school and/or work (both items not included in the SDS total score).

The SDS total score is calculated as the sum of the 3 first items and ranges from 0 (Not at all) to 30 (Extremely). If one or more items are missing at a visit, as can occur when a subject opts out of the work/school item because it does not apply, the total score will be set to missing.

16.1.1.5. Hamilton Rating Scale for Anxiety (HAM-A)

The HAM-A is a 14-item rating scale developed to quantify the severity of anxiety symptomatology, measured at Screening, Baseline, Weeks 4, 12, 20 and 28 (for subject outside Japan) and Weeks 4, 12, 20, 28, 36, 44 and 52 for subject in Japan.

The 14 items are: anxious mood, tension, fears, insomnia, intellectual, depressed mood, somatic (muscular), somatic (sensory), cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, autonomic symptoms, and behavior at interview. Each of the 14 items is rated on a 5-point scale, ranging from 0 (not present) to 4 (severe/disabling).

The HAM-A total score is the sum of the 14 individual items and ranges from 0 to 56. Higher scores are associated with a greater degree of anxiety. If one or more items are missing at a visit, the total score will be set to missing.

16.1.1.6. Time to recurrence/relapse of any mood event from clinical stability of bipolar disorder

Clinical stability is defined as a total score of <= 12 on the YMRS and the MADRS over at least 12 weeks, with the allowance of 2 excursions (the YMRS and/or MSDRS total scores up to 13 or 14, respectively) except during the last 4 weeks before achieving clinical stability.

Duration of stabilization period is defined as the time period during which subjects achieve and maintain

clinical stability during the study. If a subject experiences > 2 excursions within the projected stabilization period, the stabilization "clock" must be restarted and counting of weeks of the stabilization period will start again. The duration of the stabilization period will be calculated as: ((date of stabilization – date of first dose of study medication) +1).

Recurrence/relapse of any mood event is defined as any of the following criteria:

1. Fulfilled DSM-IV-TR criteria for major depressive, manic, mixed, hypomanic episode

2. Required treatment intervention for major depressive, manic, mixed or hypomanic episode symptoms with any antipsychotic (other than study medication), antidepressant, mood stabilizer (other than lithium or VPA), anxiolytic or benzodiazepine (beyond dosage allowed for anxiety, agitation or insomnia in the protocol)

3. Psychiatric hospitalization for any bipolar mood episode

4. YMRS or MADRS total score $\geq$ 18 or at least one of the CGI-BP-S (overall, depression, mania) scores >= 4 at two consecutive assessments no more than 10 days apart

5. Discontinuation from the study because of a mood episode (as determined by the Investigator)

Time to recurrence of any mood event from clinical stability is defined as ((date of first recurrence of any mood event – clinical stability date) + 1). Time to recurrence will be censored at the time of study completion or early termination, defined as ((date of study completion or discontinuation – clinical stability date) + 1), for subjects who discontinue or complete the study without experiencing any recurrence of mood event.

16.1.1.7. Time to All-cause Discontinuation

The time to all-cause discontinuation is defined as ((date of discontinuation – date of first dose of study medication) + 1). When a subject completes the study, the time to event is censored at the time of study completion.

16.1.2. SENSITIVITY ANALYSIS VARIABLES

16.1.2.1. Time to Recurrence of a Major Depressive, Manic, Mixed, Hypomanic Episode

Time to recurrence of a major depressive, manic, mixed or hypomanic episode is defined as ((date of first episode of any mood event – date of clinical stability) + 1). When a subject completes the study without experiencing any mood event, the time to event may be censored at the time of study completion or discontinuation.

16.1.3. MISSING DATA METHODS FOR EFFICACY VARIABLE(S)

In the event that any of the component elements of a total score are missing, the total score will be set to missing.

Missing data will be accounted for using a LOCF method to impute the Week 28 (LOCF) endpoint and the Week 52 (LOCF) endpoint values only. For calculation details, please see section 6.3.

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16.1.4. ANALYSIS OF EFFICACY VARIABLE(S)

16.1.4.1.   Analysis of MADRS, YMRS, CGI-BP-S, SDS and HAM-A

Observed and change from DB baseline and LT baseline to each post-baseline visit including Week 28 (LOCF) endpoint and Week 52 (LOCF) endpoint for subject within Japan, will be summarized for the safety population by treatment group for the following scores:

- MADRS total score

- YMRS total score

- CGI-BP-S overall score

- CGI-BP-S depression score

- CGI-BP-S mania score

- SDS total score and subscale scores of work/school, social life or leisure activities, and home life or family responsibilities, and days lost and days underproductive

- HAM-A total score

MADRS total score, YMRS total score and CGI-BP-S overall score summaries will be presented for all subjects up to Week 28 overall, by country (excluding Japan), Sex, Age and Mood Stabilizer subgroups separately, and will be repeated for all Japanese subjects up to Week 52 overall, by Sex, Age, Mood Stabilizer, Most Recent or Current Episode, Bipolar I Subtype and Psychotic Features subgroups separately as well.

CGI-BP-S depression and mania score summaries will be presented for all subjects up to Week 28 overall and by country (excluding Japan) separately, and will be repeated for all Japanese subjects up to Week 52 overall, by Sex, Age, Mood Stabilizer, Most Recent or Current Episode separately as well.

SDS total score and subscale scores and HAM-A total score summaries will be presented for all subjects up to Week 28 and repeated for all Japanese subjects up to Week 52.

16.1.4.2.   Time to recurrence/relapse of any mood event from clinical stability of bipolar I disorder

Time to recurrence/relapse of any mood event from clinical stability of bipolar I disorder will be analyzed using a time-to-event analysis. Kaplan-Meier (KM) results will be displayed for the 25%, 50% and 75% quartiles, including its 95% confidence interval using the product limit method. The KM figure will be produced to support the analysis. The time to recurrence/relapse of any mood event from clinical stability of bipolar I disorder will be presented for all subjects up to Week 28 overall, by country, Sex, Age and Mood Stabilizer separately, and will be repeated for all Japanese subjects up to Week 52 overall, by Sex, Age, Mood Stabilizer, Most Recent or Current Episode, Bipolar I Subtype and Psychotic Features separately as well.

Time to recurrence/relapse of any mood event from clinical stability of bipolar I disorder for subjects with more than 28 Weeks of treatment duration after clinical stability will also be analyzed using a time-to-event analysis and will be presented for all Japanese subjects up to Week 52.

The frequency and percentages of subjects with clinical stability as well as subject who experience a recurrence/relapse of any mood event from clinical stability will be summarized as well as the duration of stabilization which will be summarized descriptively. Summaries will be based on the safety population, by

treatment group for all subjects up to Week 28 overall and by country separately, and will be repeated for all Japanese subjects up to Week 52 separately as well.

16.1.4.3. Time to All-cause Discontinuation

Time To all-cause discontinuation will be analyzed using a time-to-event analysis. KM results will be displayed for the 25%, 50% and 75% quartiles, including its 95% confidence interval using the product limit method. The KM figure will be produced to support the analysis. Time to all-cause discontinuation will be presented for all subjects up to Week 28 overall, by country, Sex, Age and Mood Stabilizer separately, and repeated for all Japanese subjects up to Week 52 overall, by Sex, Age, Mood Stabilizer, Most Recent or Current Episode, Bipolar I Subtype and Psychotic Features separately as well.

Time to all-cause discontinuation for subjects with more than 28 Weeks of treatment duration after clinical stability will also be analyzed using a time-to-event analysis and presented for all Japanese subjects up to Week 52.

16.1.5. SENSITIVITY ANALYSIS OF EFFICACY VARIABLE(S)

16.1.5.1. Time to Recurrence of a Major Depressive, Manic, Mixed or Hypomanic Episode

Time to recurrence of a DSM-IV-TR major depressive episode will be analyzed using a time-to-event analysis. KM results will be displayed for the 25%, 50% and 75% quartiles, including its 95% confidence interval using the product limit method. The KM figure will be produced to support the analysis.

Likewise, time to recurrence of any DSM-IV-TR manic, mixed or hypomanic episode will also be analyzed in the same way. For determining the above episode types, information will be used from the protocol-defined criteria for meeting a DSM-IV-TR event.

Time to recurrence of DSM-IV-TR major depressive episode, manic, mixed or hypomanic summaries will be presented for all subjects up to Week 28 and repeated for all Japanese subjects up to Week 52 separately.

17. SAFETY OUTCOMES

All output summaries for safety outcomes will be based on the safety population. Listings will include all enrolled subjects.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

17.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 19.1. All categories of AEs will be summarized by treatment group for the safety population.

Listings will be provided of TEAEs resulting in death, serious TEAEs, and TEAEs resulting in discontinuation from the study. All three listings will use the safety population.

Treatment-emergent adverse events (TEAEs) are defined relative to Week 28 and Week 52 as follows:

- TEAEs up to Week 28 defined as:

o AEs with a start date on or after the date of first dose of study medication through 7 days after last dose of study medication (14 days for serious adverse events and deaths) for subjects outside Japan, or

o Subjects within Japan who early terminate the study prior to Week 28 will be derived based on the derivation above

o For subjects within Japan who participate in the study after Week 28, TEAEs will include AEs with a start date on or after the first dose of study medication up to Week 28

- TEAEs up to Week 52 defined as:

    o AEs with a start date on or after the date of first dose of study medication through 7 days after last dose of study medication (14 days for serious adverse events and deaths) for all subjects within Japan

All AEs with an onset date after the consent date for the long-term study but prior to the first dose in the long-term study will be summarized separately in the long-term study. Adverse events and serious adverse events (SAEs) with completely missing onset dates will be summarized as treatment emergent regardless of severity or relationship to study medication, unless the AE stop date occurs before the date of first dose of study medication.

See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

An overall summary of subjects within each of the categories described in section 17.1.1 below, will be provided as specified in the templates.

Listings will include TEAEs and Non-TEAEs.

17.1.1. ALL TEAEs

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity and relationship to study medication. Summaries will be presented for all subjects up to Week 28 overall and by country, and will be repeated for all Japanese subjects up to Week 52 separately as well.

17.1.1.1.   Severity

Severity is classed as 'mild', 'moderate' or 'severe' (increasing severity). TEAEs starting after the first dose of study medication with a missing severity will be classified as 'not specified'. If a subject reports a TEAE more than once within that SOC and PT, the AE with the worst-case severity will be used in the corresponding severity summaries. In determining maximum severity, response values will be ranked in order from minimum severity to maximum severity as values: 'not specified', 'mild', 'moderate', and 'severe'.

An additional summary will be presented for Treatment-Emergent Adverse Events Occurring in at Least 3% of Subjects broken down by maximum severity for all subjects up to Week 28 overall, and will be repeated for all Japanese subjects up to Week 52 by Most Recent or Current Episode.

17.1.1.2.   Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as 'related', 'not related' or 'not specified'. The categories of 'possible', 'probable', and 'definite' will be pooled to create the 'related' category. Similarly, 'not related' and 'unlikely' will be pooled to create the 'not related' designation. If a subject has more than one AE

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within an SOC and PT, the subject will be counted once according to the highest relationship. Adverse events with missing relationship will be classified as 'not specified'. In determining highest relationship, response values will be ranked in order from minimum relationship to maximum relationship as values: 'not specified', 'not related', and 'related'.

An additional summary will be presented for Treatment-Emergent Adverse Events Occurring in at Least 3% of Subjects broken down by relationship to study medication for all subjects up to Week 28 overall.

17.1.2. TEAEs LEADING TO DISCONTINUATION OF STUDY MEDICATION

TEAEs leading to permanent discontinuation of study medication will be identified by using the 'action taken' variable collected on the eCRF.

For TEAEs leading to discontinuation of study medication, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared. A listing will provide details of these TEAEs and indicate any drug relationship.

17.1.3. SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the eCRF. A summary of serious TEAEs by SOC and PT will be prepared. A listing will provide details of SAEs and indicate any drug relationship.

17.1.4. ADVERSE EVENTS LEADING TO DEATH

TEAEs leading to Death are those events which are recorded as "Fatal" on the Adverse Events page of the eCRF. These events will be listed.

17.1.5. ADVERSE EVENTS OF SPECIAL INTEREST

17.1.5.1. TEAEs relating to Extrapyramidal Symptoms
The overall incidence of TEAEs relating to Extrapyramidal symptoms (EPS) will be summarized by Preferred Term and treatment group. These will be identified by using a list of specified terms from medical personnel, which can be found in Appendix 3. This summary will be repeated for all Japanese subjects up to Week 52 separately as well.

17.1.5.2. Metabolic TEAEs
The overall incidence of Metabolic TEAEs will be summarized by Preferred Term and treatment group. These will be identified by using a list of specified terms from medical personnel, which can be found in Appendix 3. This summary will be repeated for all Japanese subjects up to Week 52 separately as well.

17.1.5.3. Mood event-related TEAEs
The overall incidence of mood event-related TEAEs will be summarized by Preferred Term and treatment group. These will be identified by using a list of specified terms from medical personnel, which can be found in Appendix 3. This summary will be repeated for all Japanese subjects up to Week 52 overall, by Mood Stabilizer and by Most Recent or Current Episode subgroups separately as well.

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17.1.6. SUBGROUP ANALYSIS OF ADVERSE EVENTS

An overall summary of adverse events will be presented for all subjects up to Week 28 overall and by country, and repeated for all Japanese subjects up to Week 52 overall, by Sex, Age, Mood Stabilizer and Most Recent or Current Episode subgroups separately as well.

Other adverse event summaries will be repeated for all Japanese subjects up to Week 52 separately as noted in the appropriate sections.

17.1.7. ADDITIONAL AE SUMMARIES

17.1.7.1.   AEs by exposure interval at earliest onset

AEs will be summarized by SOC and PT by exposure intervals. If there are multiple occurrences of one TEAE, only the first incidence will be summarized. Denominators for exposure intervals will be based on the number of subjects who were exposed as of the first day of the interval. For cases where the events meet the treatment-emergent definition but start after the last dose of study medication, the exposure interval for the event will be considered the interval of the last day of exposure to study medication.

Exposure categories to be assessed are the following:

- For all subjects up to Week 28: 1-56 days, 57-112, 113-168 and >= 169 days.

- For all Japanese subjects up to Week 52: 1-56 days, 57-112, 113-168, 169-224, 225-280, 281-336 and >= 337 days.

An additional summary will be presented for Treatment-Emergent Adverse Events Occurring in at Least 3% of Subjects broken down by exposure categories for all subjects up to Week 28 overall.

17.1.7.2.   TEAEs ≥ 3%

A summary of TEAEs with an incidence of ≥3% of subjects will be presented by Preferred Term and treatment group. Summaries will be provided for the safety population. This summary will be repeated separately for all Japanese subjects up to Week 52 of TEAEs with an incidence of ≥3% of subjects, and repeated by Most Recent or Current Episode subgroup separately as well.

17.1.7.3.   Combined PTs

A summary of TEAEs by combined PT will be presented by SOC and PT, where combined PT will be determined by medical review of coded AE terms prior to database lock. The list of combined PT can be found in Appendix 3. This summary will be repeated for all Japanese subjects up to Week 52 separately as well.

17.1.7.4.   AEs by PT by descending frequency

A summary of AEs by PT by descending frequency will be presented by treatment group. This summary will be repeated for all Japanese subjects up to Week 52 separately as well.

17.2. DEATHS

If any subjects died during the study, the information will be presented in a data listing. Deaths will be recorded on either the AE panel as an AE leading to death ("Fatal" AE), or on the C-SSRS panel as a lethal suicide attempt.

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17.3. LABORATORY EVALUATIONS

Results from the central laboratory will be included in the reporting of this study for Hematology, Blood Chemistry and Urinalysis. Endocrine parameters will be summarized separately. A list of laboratory assessments to be presented in the outputs is included in Table 8 of the protocol. Laboratory data will be summarized for the safety population by treatment group.

Presentations will use reported units, except for Chloride, Potassium and Sodium that will use SI Units (International System of Units).

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries will be provided for laboratory data:

- Observed and change from DB baseline and LT baseline to each post-baseline visit including Week 28 (LOCF) endpoint and Week 52 (LOCF) endpoint for subjects within Japan (for quantitative measurements)

- Shift from DB baseline and LT baseline to Week 28 (LOCF) and Week 52 (LOCF) endpoints according to normal range criteria (for quantitative measurements and categorical measurements)

- Summary of subjects meeting markedly abnormal criteria

- Listing of subjects meeting markedly abnormal criteria

The following parameters are presented split by fasting status and overall: HDL cholesterol, LDL cholesterol, total cholesterol, insulin, triglycerides, glucose and homeostasis model assessment of insulin resistance (HOMA-IR). For laboratory variables split by fasting, change from DB baseline and LT baseline will only be calculated where the post-baseline fasting status matches the DB baseline or LT baseline fasting status respectively. Fasting parameters will only be summarized at DB Baseline, LT Baseline, Week 28 and Week 28 (LOCF) visits and at Week 52 and Week 52 (LOCF) for subjects within Japan.

Prolactin will be presented overall and by sex.

17.3.1. LABORATORY SPECIFIC DERIVATIONS

A homeostasis model assessment of insulin resistance (HOMA-IR) (Matthews, Hosker, Rudenski, Naylor, Treacher, & Turner, 1985) parameter must also be calculated and included in summaries. The calculation of the parameter is as follows:

HOMA-IR = Glucose (mg/dL) x Insulin (mU/L) / 405

17.3.2. LABORATORY REFERENCE RANGES AND MARKEDLY ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.

- Normal: Within the laboratory reference range (upper and lower limit included).

- High: Above the upper limit of the laboratory reference range.

In addition to the high and low quantitative laboratory assignments (as identified by means of the laboratory reference ranges), markedly abnormal quantitative safety (and other) laboratory assessments will also be identified. Markedly Abnormal Post-Baseline Laboratory Values (MAPLV) for selected laboratory parameters can be found in Table C. The criterion of MAPLV is satisfied if a value falls into the markedly abnormal range. Subjects will be represented in the count of a particular MAPLV if they have experienced that MAPLV at least once during the post-baseline treatment phase, regardless of baseline value, up to and including LOCF endpoints. The number and percentage of subjects with MAPLV will be presented by treatment group for all subjects up to Week 28 overall and repeated for all Japanese subjects up to Week 52 overall separately as well.

Table C: **Criteria for Markedly Abnormal Post-Baseline Laboratory Values**

Hematology Parameter	Markedly Abnormal Range
Hemoglobin	Male: ≤ 11.5 g/dL
	Female: ≤ 9.5 g/dL
Hematocrit	Male: ≤ 37%
	Female: ≤ 32%
WBC	≤ 2.8 x 10⁹/L
	≥ 16 x 10⁹/L
Neutrophils (percent)	≤ 15%
Eosinophils (percent)	≥ 10%
Platelet Count	≤ 75 x 10⁹/L
	≥ 700 x 10⁹/L
Clinical Chemistry Parameter	**Markedly Abnormal Range**
Alkaline Phosphatase	≥ 3 x ULN
ALT	≥ 3 x ULN
AST	≥ 3 x ULN
Bilirubin	≥ 2.0 mg/dL
Albumin	< 50% LLN
Glucose (fasting)	< 45 mg/dL
	>160 mg/dL
Sodium	< 130 mmol/L
	> 150 mmol/L
Potassium	< 3 mmol/L
	> 5.5 mmol/L
Chloride	< 90 mmol/L
	> 115 mmol/L
Blood Urea Nitrogen	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Creatinine Phosphokinase	≥ 3 x ULN
HbA1c	≥ 7.5%
Prolactin	≥ 5 x ULN
Lactate Dehydrogenase	≥ 3 x ULN
Total Cholesterol (fasting)	≥ 300 mg/dL
LDL Cholesterol (fasting)	≥ 200 mg/dL
Triglycerides (fasting)	≥ 300 mg/dL

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17.3.3. SUBGROUP ANALYSIS OF LABORATORY VALUES

The following laboratory parameters will be evaluated for the subgroups specified in section 7.5: serum prolactin, blood glucose, HOMA-IR, HbA1c (NGSP), glycoalbumin (absolute and percentage), total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides. These parameters will be separated by fasting status (as applicable) for the subgroup analyses.

Observed and change from DB baseline and LT baseline summaries for clinical chemistry and hematology parameters will be presented for all subjects up to Week 28 overall and by country (excluding Japan) separately, and repeated for all Japanese subjects up to Week 52 separately as well. For the above selected clinical chemistry parameters the observed and change from DB baseline and TL baseline summaries will be repeated for all subjects up to Week 28 by Sex subgroup, all Japanese subjects up to Week 52 by Sex, Age and Mood Stabilizer subgroups separately as well.

Shifts from DB baseline and LT baseline summaries for clinical chemistry and hematology parameters will be presented for all subjects up to Week 28 and repeated for all Japanese subjects up to Week 52 as well. Shift from DB baseline and LT baseline for Prolactin will be presented overall and by Sex.

Number and percentage of MAPVL summaries will be presented for all subjects up to Week 28 overall and will be repeated for all Japanese subjects up to Week 52 separately as well.

17.4. ECG EVALUATIONS

Results from the central ███████████████ will be included in the reporting of this study. ECG results will be summarized by treatment group for the safety population.

A Week 28 (LOCF) endpoint and Week 52 (LOCF) endpoint (only for subjects in Japan) will also be derived for ECG. For calculation details, please see section 6.3.

The following ECG parameters will be reported for this study:

- Heart Rate (bpm)

- PR Interval (msec)

- QRS Interval (msec)

- QT Interval (msec)

- QTcB Interval (msec): QTc Interval using Bazett's correction

- QTcF Interval (msec): QTc Interval using Fridericia's correction

- RR Interval (msec)

- Overall assessment of ECG (Investigator's judgment):
  o Normal
  o Abnormal

The following summaries will be provided for ECG data:

- Observed, DB baseline and LT baseline and change from DB baseline and LT baseline by visit (for quantitative measurements)

- Shift from DB baseline and LT baseline to Week 28 (LOCF) and Week 52 (LOCF) endpoints according to abnormal criteria (for overall assessment)

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- Summary of subjects with abnormal ECG values (see section 17.4.2)

- Incidence of QTc Prolongation (see section 17.4.3)

- Listing of subjects with prolonged QTc results

17.4.1. ECG SPECIFIC DERIVATIONS

All required ECG parameters are available in the data provided for analysis. There are no ECG parameters to be derived.

17.4.2. ECG ABNORMAL CRITERIA

The individual ECG measurements would be noted as abnormal if exceeding the values indicated in Table D.

Table D: **Abnormal ECG Values by parameter**

ECG Parameter	Abnormal
HR (bpm)	≥ 100 bpm
PR interval (msec)	≥ 210 msec
QRS interval (msec)	≥ 120 msec
QT interval (msec)	> 500 msec

17.4.3. ECG MARKEDLY ABNORMAL CRITERIA (QTC PROLONGATION)

Markedly abnormal quantitative post-baseline ECG measurements will be identified in accordance with the following predefined markedly abnormal criteria:

- Absolute values for QTcB interval and QTcF will be classified as:

  o   Male > 450 msec or Female > 470 msec
  o   > 450 msec
  o   > 480 msec
  o   > 500 msec

- Change from Baseline for QTcB interval and QTcF will be classified as:

  o   ≥ 30 msec increase from baseline
  o   ≥ 60 msec increase from baseline

17.4.4. SUBGROUP ANALYSIS OF ECG PARAMETERS

The following laboratory parameters will be evaluated for the subgroups specified in section 7.5: QTcB interval and QTcF interval.

Observed, DB baseline and LT baseline and change from D8 baseline and LT baseline at Weeks 28 and 28 (LOCF) analyses will be repeated for all subjects up to Week 28 overall and by country (excluding Japan), and

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repeated at Weeks 52 and 52 (LOCF) for all Japanese subjects up to Week 52 overall, by Sex, Age and Mood Stabilizer subgroups separately as well.

Shifts from DB baseline and LT baseline, abnormal ECG values as well as prolonged QTc values will be repeated for all subjects up to Week 28 as well as all Japanese subjects up to Week 52 separately as well.

17.5. VITAL SIGNS

Vital sign results as recorded of the eCRF will be included in the reporting of this study, and will be summarized by treatment group for the safety population.

A Week 28 (LOCF) endpoint and Week 52 (LOCF) endpoint (only for subjects in Japan) will also be derived for Vital Signs. For calculation details, please see section 6.3.

The following Vital Signs measurements will be reported for this study:

- Pulse Rate (bpm)

- Systolic Blood Pressure (mmHg)

- Diastolic Blood Pressure (mmHg)

- Body Temperature (C)

- Weight (kg)

- BMI (kg/m^2)

The following summaries will be provided for vital signs data:

- Observed, DB baseline and LT baseline and change from DB baseline and LT baseline by visit

- Incidence of markedly abnormal values (see section 17.5.2)

- Shift from DB baseline and LT baseline to Week 28 (LOCF) and Week 52 (LOCF) endpoints for Body Mass Index (BMI) according to the categories Underweight (BMI < 18.5 kg/m^2), Normal (18.5 ≤ BMI < 25 kg/m^2), Overweight (25 ≤ BMI < 30 kg/m^2) and Obese (BMI ≥ 30 kg/m^2).

- Listing of subjects meeting markedly abnormal post-baseline vital signs (MAPVS) criteria (see section 17.5.2)

17.5.1. VITAL SIGNS SPECIFIC DERIVATIONS

BMI (kg/m^2) = Weight (kg)/Weight (m) ^{2}.

17.5.2. VITAL SIGNS MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the following predefined markedly abnormal criteria indicated in Table E.

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Table E: **Criteria for Markedly Abnormal Vital Signs**

Variable	Unit	Low	High
Pulse rate	Bpm	≤ 50 bpm AND change from baseline ≤ -15 bpm	≥ 120 bpm AND change from baseline ≥ 15 bpm
SBP	mmHg	≤ 90 mmHg AND change from baseline ≤ -20 mmHg	≥ 180 mmHg AND change from baseline ≥ 20 mmHg
DBP	mmHg	≤ 50 mmHg AND change from baseline ≤ -15 mmHg	≥ 105 mmHg AND change from baseline ≥ 15 mmHg
Body temperature	°C	NA	≥ 38.3 °C AND change from baseline ≥ 0.8 °C
Weight	Kg	percentage change from baseline ≤ -7.0 %	percentage change from baseline ≥ 7.0 %

17.5.3. SUBGROUP ANALYSIS OF VITAL SIGNS VALUES

Observed, DB baseline and LT baseline and change from DB baseline and LT baseline by visit analyses will be repeated for all subjects up to Week 28 and repeated for Japanese subjects up to Week 52 separately as well.

For weight and BMI measurements only, summaries for observed, DB baseline and LT baseline and change from DB baseline and LT baseline at Weeks 28 and 28 (LOCF) will be repeated for all subjects up to Week 28 overall and by country (excluding Japan) as well as at Weeks 52 and 52 (LOCF) for all Japanese subjects up to Week 52 overall, by Sex, Age and Mood Stabilizer subgroups separately as well.

Incidence of markedly abnormal post LT baseline vital signs (MAPVS) will be repeated for all subjects up to Week 28 as well as for all Japanese subjects up to Week 52 separately as well.

17.6. PHYSICAL EXAMINATION

Physical Examination results will be listed.

17.7. OTHER SAFETY ASSESSMENTS

17.7.1. DRUG-INDUCED EXTRAPYRAMIDAL SYMPTOM SCALE (DIEPSS)

The DIEPSS is a clinician-rated assessment of extrapyramidal symptoms induced by antipsychotics and consists of eight individual parameters; gait, bradykinesia, sialorrhea, muscle rigidity, tremor, akathisia, dystonia and dyskinesia; and one global assessment; overall severity. The severity of each item is graded 0 (normal) to 4 (severe), and then a summation of all questions (excluding overall severity) provides the total score, ranging from 0 to 32, which is used for analysis. The investigator will assess the DIEPSS at Week 1 to Week 28 and Week 52 (subjects within Japan) and at discontinuation. The assessment at Week 28, Week 52 or at discontinuation should be performed within 72 hours after the final administration of the study and before the initiation of post treatment with antipsychotics.

A Week 28 (LOCF) endpoint and Week 52 (LOCF) for subjects within Japan will also be derived for DIEPSS. For calculation details, please see section 6.3.

17.7.1.1.   Missing Data Methods

Missing question data for questionnaires is accounted for in the variable descriptions. The methods used for analysis of this endpoint will address visit data that is missing. In the event that any component element of the total score (excluding overall severity) is missing, then this total score will be set to missing.

17.7.1.2.   Analysis of DIEPSS

Observed, DB baseline and LT baseline and change from DB baseline and LT baseline in the DIEPSS total score (excluding overall severity) and the individual DIEPSS scores by visit as well as Week 28 (LOCF) endpoint and Week 52 (LOCF) for subjects within Japan will be summarized for the safety population by treatment group.

17.7.1.3.   Subgroup Analysis of DIEPSS

Observed, DB baseline and LT baseline and change from DB baseline and LT baseline at Weeks 28 and 28 (LOCF) analyses will be repeated for all subjects up to Week 28 overall and by country (excluding Japan) and separately at Weeks 52 and 52 (LOCF) for Japanese subjects up to Week 52 overall, by Sex, Age and Mood Stabilizer, only for DIEPPS total score (excluding overall severity).

17.7.2. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

The C-SSRS is a tool designed to systematically assess and track suicidal adverse events (suicidal behavior and suicidal ideation) throughout the study. The C-SSRS can comprehensively identify suicidal events and limit the over-identification of suicidal behavior. The rater will assess the C-SSRS at Day 1 to Week 28 and Week 52 (subjects within Japan) and at discontinuation. The 'baseline/screening' version will be used at Day 1 for subjects who did not participate in the prior double-blind study, and the 'since last visit 'version at Week 1 to Week 28, Week 52 and at discontinuation will be used for all subjects. The assessment at Week 28, Week 52 or at discontinuation should be performed within 72 hours after the final administration of the study medication and before the initiation of post treatment with antipsychotics.

Suicidal ideation is rated on a 6-point scale from 0='No ideation present' to 5='Active ideation with plan and intent'. A score of 4 or 5 on this scale indicates serious suicidal ideation. Intensity of ideation is measured in terms of frequency, duration, controllability, deterrents, and reasons for ideation. Each is measured with responses ranging from 0 or 1 to 5, representing approximately less to more. The ideation intensity total score is the sum of the five preceding items and can range from 3 to 25 for subjects with suicidal ideation endorsed.

Suicidal behavior is collected as presence/absence of actual attempts, non-suicidal self-injurious behavior, interrupted attempts, aborted attempts, preparatory acts or behavior, and any suicidal behavior. In addition, the number of actual attempts, interrupted attempts, and aborted attempts is captured. Any attempt will be defined as suicidal behavior. The lethality associated with actual attempts is rated on a 6-point scale from 0='No physical damage or very minor physical damage' to 5='Death'. Potential lethality of attempts is rated on a 3-point scale from 0='Behavior not likely to result in injury' to 2='Behavior likely to result in death despite available medical care'.

A composite measure of suicidality measures the presence of any suicidal ideation or behavior.

The number and percentage of subjects with suicidality as measured by the C-SSRS will be summarized, where suicidality is defined as having at least one occurrence of suicidal ideation or at least one occurrence of suicidal behavior. The LT baseline suicidality indicator will be set to 1 if the subject exhibits suicidality during the two weeks prior to the LT baseline visit, 0 if the subject does not exhibit suicidality during the two weeks prior to the LT baseline visit, and missing otherwise. The post LT baseline suicidality indicator is similarly defined for each post LT baseline visit.

17.7.2.1. Analysis of C-SSRS

A summary by Visits for all subjects up to Week 28 as well as all Japanese subjects up to Week 52 separately will include the frequency and percentage of the following for the safety population, by treatment group:

- Suicidal Ideation

- Suicidal Behavior

- Suicidality: any suicidal ideation or behavior

An overall summary of post LT baseline data across visits up to and including Week 28 and Week 52 endpoint will include the frequency and percentage of the previous 3 overall items for the safety population, by treatment group.

17.7.2.2. Subgroup Analysis of C-SSRS

The overall summary of post LT baseline data across visits will be presented for all subjects up to Week 28 as well as all Japanese subjects up to Week 52 separately. All Japanese subjects up to Week 52 by Mood Stabilizer and Most Recent or Current Episode subgroups will be summarized separately as well.

18. ADDITIONAL SUMMARIES BY MAJOR VS. NON-MAJOR DEPRESSIVE EPISODE

A set of additional summaries will be presented for Japanese subjects regarding their most recent or current episode of Bipolar I Disorder, classed as Major vs Non-Major Depressive Episode. These tables will include all Japanese subjects (both subjects who completed the prior double-blind study as well as newly recruited subjects for the extension study) overall and by episode, splitting by presence or absence of a major depressive episode, and in case of a non-major depressive episode, by episode type (manic, mixed or hypomanic).

The tables to be included contain summaries of the following data:

- Disposition data.

- Demographics and other baseline characteristics, including psychiatric and medical history, prior and concomitant medications.

- Treatment exposure and compliance, as well as Lithium and VPA exposure.

- Efficacy data: MADRS and YMRS Total Scores, Summary of Recurrence/Relapse Criteria and Time to Recurrence/Relapse of any Mood Event from Clinical Stability, and Time to All-Cause Discontinuation.

- Safety data: Adverse Events and C-SSRS overall summary.

19. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Comments

- MINI screening questionnaire

These domains and/or variables will not be summarized or presented, but will be available in the clinical study

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database, SDTM and/or ADaM datasets.

20. REFERENCES

Allison, P. (2010). Missing Data. In P. Marsden, & J. Wright, *Handbook of Survery Research* (pp. 631-657). Bingley, UK: Emerald Group Publishing Ltd.

Matthews, D., Hosker, J., Rudenski, A., Naylor, B., Treacher, D., & Turner, R. (1985). Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* , 412-419.

Stokes, M., Davis, C., & Koch, G. (1995). *Categorical Data Analysis using the SAS system.* Cary, NC: SAS Institute Inc.

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APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

OUTPUT CONVENTIONS

Outputs will be presented according to the following conventions, which follow Sumitomo output conventions but use information from previous SM-13496 study layout:

1. ABBREVIATIONS

ASCII   American standard code for information interchange file format

CGM   Computer graphics metafile

ODS   Output Delivery System

RTF   Rich text file format

2. INTRODUCTION

This document applies to standards used for outputting tables, listings and figures. It is intended to provide specifications to guide the statistician or statistical programmer in setting up specifications for programming tables, listings and figures.

3. OUTPUT FILE NAMING CONVENTIONS

File names should only consist of lowercase letters, digits (0 to 9) and dashes. A period should only be used to indicate a separator between the file name and the extension. No spaces, other special characters or punctuation marks are permitted. As dashes are not permitted in SAS program names, they will be replaced with underscores

Output files should be in RTF format.

The program, program log and output file name should reflect the type and number of the statistical output. If this is not possible, then the output name should be at least as descriptive as possible. A prefix can be used to distinguish between a Table, Listing and Figure document ('t' for table, 'l' for listing and 'f' for figure). If there is only 1 digit in the number of the table, listing or figure in the place where 2 digits are possible, a leading zero should be added in the file name to make sorting consistent with the sequence (e.g. t14_3_01_1.RTF)

4. PAPER SIZE, ORIENTATION AND MARGINS

- The size of paper will be A4.

- The page orientation should preferably be landscape, but portrait is also permitted.

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- Margins should provide at least 3 centimeters of white space all around the page, regardless of the paper size.

- The number of columns per page (linesize) should be 132 for A4.

- The number of rows per page (pagesize) should be 46 for A4.

5. FONTS

The font type 'Times New Roman' should be used as a default for tables and listings, with a font size of 9. The font color should be black. No bolding, underlining italics or subscripting should be permitted. Try to avoid using super-scripts, unless absolutely necessary. Single spacing should be used for all text.
Figures should have a default font of "Times Roman", "Helvetica", or "Courier New".
This can be achieved by using the following options in SAS:

```
goptions
gunit = pct
cback = white
colors = (black)
hby = 2.4
ftext = "TimesRoman"
htext = 2.5
device = cgmof971
gaccess = gsasfile;
filename gsasfile "....cgm";
```

6. HEADER INFORMATION

Headers should be defined as follows:

- The header should be placed at the top of the page (same place on each page) regardless of the size or orientation of the table or listing

- The customer name and protocol number should appear in row 1, left-aligned

- The output identification number should appear in row 2, centered

- The output title should start in row 3, centered

- The output population should appear in row 4, centered. The population should be spelled out in full, e.g. All Enrolled Population and Safety Population.

- Row 5 should be a continuous row of underscores ('_') (the number of underscores should equal the linesize)

- Row 6 should be a blank line

- Mixed case should be used for titles

- The output titles should be designed so that they are arranged consistently through all outputs. For example, content (e.g. Vital Signs) followed by metric (e.g. Change from Baseline) e.g. Vital Signs – Change from Baseline.

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Titles should not contain quotation marks or footnote references.

- Titles will only appear on the first page of the outputs

- The column headings should be underlined with a row of underscores ('_')

- Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered

- Column headings containing numbers should be centered

- Column headings should be in proper case

- In general, the population count should appear in the column header in the form "(N=XXX)"

- "Statistic" should be the column header over n, Mean, SE, n (%) etc.

- As a rule, all columns should have column headings

- The header of the output will be in a non-selectable format for all pages after page one

7. TABLE AND LISTING OUTPUT CONVENTIONS

General:

- The first row in the body of the table or listing should be blank

- The left-hand column should start in column 1. No indenting or centering of the output should occur

- Rounding should be done with the SAS function ROUND

- Numbers in tables should be rounded, not truncated

- Alphanumeric output should be left aligned

- Numbers should be decimal point aligned

- Whole numbers should be right aligned

- Text values should be left aligned

- The first letter of a text entry should be capitalized

- Listings of adverse events, concomitant medications, medical histories etc. should be sorted in chronological order, with earliest adverse event, medication or history coming first

- Placebo should appear first in tables with treatments as columns

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- In general, only present totals (across treatment groups) at baseline/randomization, and do not present them post randomization, unless the customer specifically requests it

- If possible, include 100% frequencies in the table shell, so that it is clear what the denominator is for percentage calculations

- All listing outputs should be sorted (preferably by Treatment, Site Number and Subject Number)

- Exponentiation will be expressed using a double asterisk, i.e., mm3 will be written as mm**3

- All variables that are output in the CRF (which have data present) should appear in the listings, along with all derived data appearing in the corresponding tables

- The width of the entire output should match the linesize

Univariate Statistics:
- Statistics should be presented in the same order across tables (i.e., n, Mean, SD, Median, Minimum, Maximum)
- Table statistics should line up under the N part of the (N=XXX) in the table header. All decimal points should line up. If the minimum and maximum are output on one line as Minimum, Maximum then the comma should line up with the decimal point. It is accepted that using the Times New Roman font there will be limitations to this, though it will be followed as far as is possible.
- If the original data has N decimal places, then the summary statistics should have the following decimal places:
    - Minimum and maximum: N
    - Mean, median and CV%: N + 1
    - SD: N + 2

    The only exception, as per Sponsor requirement, will be the summary statistics for CGI-BP-S Scores and DIEPSS Score, which have N=0 decimal places in the original data but will be treated as N=1 decimal place (i.e. one more decimal place will be displayed).

Frequencies and percentages (n and %):

- Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:

<div align="center">

77 (100.0%)
50 (64.9%)
0 (0.0%)

</div>

- Percentages will be reported to one decimal place, except percents <100.0% but >99.9% will be presented as '>99.9%' (e.g., 99.99% is presented as >99.9%); and percents < 0.1% will be presented as '<0.1%' (e.g., 0.08% is presented as <0.1%). Rounding will be applied after the <0.1% and >99.9% rule

<div align="center">

e.g. (<0.1%)
(6.8%)
(>99.9%)

</div>

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- Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small)

- Where counts are zero, percentages will not appear in the output

Confidence Intervals:

- As a rule, confidence intervals are output to one place more than the raw data, and standard deviations and standard errors to two places more than the raw data

- Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up"

- Boundary values of confidence intervals should be separated by a comma

- Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place

- An example is given below:

$$(-0.12, -0.10)$$
$$(\ 9.54, 12.91)$$

P-values:

- P-values should be reported to three decimal places, except values <1.000 but >0.999 will be presented as '>0.999' (e.g., 0.9998 is presented as >0.999); and values <0.001 will be presented as '<0.001' (e.g., 0.0009 is presented as <0.001). Rounding will be applied after the <0.001 and >0.999 rule

Ratios:

- Ratios should be reported to one more decimal place than the original data

Spacing:

- There must be a minimum of 1 blank space between columns (preferably 2)

Denominators:

- If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "n"

- Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages

Missing values:

- A "0" should be used to indicate a zero frequency

- A blank will be used to indicate missing data in an end-of-text table or subject listing

- In the case that only a single value is used in the creation of summary statistics (i.e. n=1) then only n and the mean will be presented.

8. FIGURE OUTPUT CONVENTIONS

- Figures should be provided in RTF files using the SAS Output Delivery System (ODS), as Computer Graphics Metafile (CGM) formatted graphical output generated by SAS.

- The CGM file itself should contain the title or footer.

- The image should be clear and of high quality when viewed in the Word document, and when printed.

- In general, boxes around the figures should be used.

9. FOOTNOTE INFORMATION

Footers should be defined as follows:

- A continuous line of underscores ('_') will follow the body of the table or listing prior to any footnotes at the bottom of the page

- Footnotes will only appear on the last page of the output

- The program path and name and version number (if applicable) as well as the date/time stamp should appear as footnote 1 at the bottom of the page

- Footnotes should be left-aligned

- Footnotes should be in sentence case

- Superscripts are used for footnotes linking to the body of the table

- The choice of footnote symbols should be consistent. E.g. if you have the footnote "# indicates last observation carried forward" for one table, the same symbol and footnote should indicate LOCF for all tables

- If text wraps across more than one line (for a note), the first letter for all lines of text after the first one will be indented to align beneath the first letter of the text in the first line

- The page identification in the format Page X of Y (where Y is the total number of pages for the output) will appear at the top of the page, right aligned

- Common notes from table to table should appear in the same order.

- The symbols should appear in the same order as what they are defined in the table or listing, from left to right.

10. PROGRAMMING INSTRUCTIONS

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Programming instructions must appear in blue font at the end of each table or listing shell. Programming instructions, where necessary, should follow the table or listing shells in blue font, beginning with the words "Programming Note" followed by a colon. These include notes on the output, reminders of how to handle missing values, repeat shells for similar tables etc.

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

SPELLING FORMAT

English US will be used.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

Treatment Group of Prior Double-blind Study	Treatment Group Long-term Study	For Tables and Graphs	For Listings (include if different to tables)
Placebo	Lurasidone (20-120 mg/day)	PBO-LUR	PBO-LUR
SM-13496 20 to 60 mg/day	Lurasidone (20-120 mg/day)	LUR20-LUR	LUR20-LUR
SM-13496 80 to 120 mg/day	Lurasidone (20-120 mg/day)	LUR80-LUR	LUR80-LUR
All dose levels of SM-13496	Lurasidone (20-120 mg/day)	LUR-LUR	LUR-LUR
Did not participate in prior study	Lurasidone (20-120 mg/day)	NR-LUR	NR-LUR
All treatment groups	Lurasidone (20-120 mg/day)	ALL-EXT	ALL-EXT
	Screen Failure		NOT TREATED

LUR: Lurasidone. PBO: Placebo. 20: 20mg/day. 80: 80 mg/day. NR: New Recruit. EXT: Long-term extension study.

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Document: K:\DSP\SM-13496\RVA97109\Biostatistics\Documentation\SAP
Author: ████████   Version Number: 1.0
Version Date: 20MAR2018

Template No: CS_TP_BS016 – Revision 3   Reference: CS_WI_BS005
Effective Date: 01May2012

Long Name (default)	Short Name
Screening	Scr
Double-blind Baseline	DB
Long-term Baseline	LT
Week 1	W1
Week 2	W2
Week 4	W4
Week 8	W8
Week 12	W12
Week 16	W16
Week 20	W20
Week 24	W24
Week 28	W28
Week 28 (LOCF)	W28LOCF
Week 32	W32
Week 36	W36
Week 40	W40
Week 44	W44
Week 48	W48
Week 52	W52
Week 52 (LOCF)	W52LOCF

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

A combination of randomized treatment group according to prior study and treatment group in long-term study in the following order: PBO-LUR, LUR20-LUR, LUR80-LUR, NR-LUR, NOT TREATED (applicable for all Screen-failure subjects),

- center-subject ID,
- visit (where applicable),
- date (where applicable).

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHMS OF PARTIAL DATES FOR AES AND MEDICATIONS

Partial dates for AEs and medications will be imputed as follows:

Adverse event or prior/concomitant medication start date (references to year and month refer to the year and month of the start date, respectively):

1. If year and month are known, and it is the month of the first dose date and the stop date is prior to the first dose date, use the first day of the month.
2. If year and month are known, and it is the month of the first dose date and the stop date is the same as or later than the first dose date, use the first dose date.
3. If year and month are known, and it is the month following the first dose date, use the first day of the month.
4. If year and month are known and it is any month prior to first dose date, use the first day of the month.
5. If only year is known, and it is previous to the year of the first dose date, use June 30th of that year. If it is the same as first dose date year, assume it is the first dose date. If it is later than the first dose date year, assume it is the first day of the year.
6. If the start date is completely missing, use the first dose date.
7. Should any of the previous start dates created be after a complete stop date provided, use the stop date instead of the date that would otherwise be created.
8. Otherwise, if start date is unknown leave as missing.

Adverse event or prior/concomitant medication stop date (references to year and month refer to the year and month of the stop date, respectively):

1. If year and month are known and study medication stopped during that month, use the stop date of study medication.
2. If year and month are known and study medication stopped after that month, use the last day of the month.
3. If year and month are known and study medication stopped prior to that month, use the first day of the month.
4. If only year is known, and it is the same as last dose date year, assume it is the last dose date. If it precedes the last dose date year, assume it is the last day of the year. If it is later than the last dose date year, assume it is the first day of the year.
5. If stop date is unknown and continuing is checked, set to date of last double-blind dose.
6. Should any of the previous stop dates created come before a start date, either a complete date or an imputed one, use the start date instead of the date that would otherwise be created.
7. Otherwise, if stop date is unknown leave as missing.

ALGORITHM FOR PARTIAL DATES IN MEDICAL HISTORY

Partial dates for medical history (including psychiatric history) will be imputed as follows:

Document:	K:\DSP\SM-13496\RVA97109\Biostatistics\Documentation\SAP		
Author:	▮▮▮	Version Number:	1.0
		Version Date:	20MAR2018

Template No: CS_TP_BS016 – Revision 3   Reference: CS_WI_BS005
Effective Date: 01May2012

Medical history start date (references to year and month refer to the year and month of the start date, respectively):

1. If year and month are known, and it is the year or month previous to Screening, use the last day of the month.
2. If year and month are known, and it is the month of Screening, use Screening date – 1.
3. If only year is known, and it is previous to the year of Screening, use June 30th of that year.
4. If only year is known, and it is the year of Screening, use Screening date – 1.

APPENDIX 3. MEDICAL REVIEW OF TERMS

EPS Terms	Metabolic Terms	Combined Terms	Treatment Emergent Mania Terms	Mood Event Terms
Muscle rigidity	Blood cholesterol increased	Parkinsonism:	Bipolar disorder	Disease progression
Trismus	Blood glucose increased	Muscle rigidity,	Euphoric mood	Apathy
Bradykinesia	Blood insulin increased	Bradykinesia,	Hypomania	Bipolar disorder
Dystonia	Blood triglycerides increased	Parkinsonism,	Mania	Depression
Parkinsonism	Fructosamine increased	Tremor,		Euphoric mood
Tremor	Glucose urine present	Psychomotor retardation		Hypomania
Psychomotor retardation	High density lipoprotein decreased	Dystonia: Dystonia, Trismus		Intentional self-injury
	Lipids abnormal	Somnolence:		Listless
	Low density lipoprotein increased	Hypersomnia, Sedation,		Mania
	Weight increased	Somnolence		Self-injurious ideation
	Diabetes mellitus			Suicidal ideation
	Dyslipidaemia			Suicide attempt
	Glucose tolerance impaired			
	Hypercholesterolaemia			
	Hyperglycaemia			
	Hyperinsulinaemia			
	Hyperlipidaemia			
	Hypertriglyceridaemia			
	Metabolic disorder			